Public Health Goal for
TRICHLOROFLUOROMETHANE
(FC-11)
in Drinking Water

Prepared by

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December 1997

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We thank the U.S. EPA's Office of Water, Office of Pollution Prevention and Toxic Substances, and National Center for Environmental Assessment for their peer review of the PHG documents, and the comments received from all interested parties.

PREFACE

Drinking Water Public Health Goal of the
Office of Environmental Health Hazard Assessment

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. The PHG describes concentrations of contaminants at which adverse health effects would not be expected to occur, even over a lifetime of exposure. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires OEHHA to adopt PHGs that meet the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which scientific evidence indicates that no known or anticipated adverse effects on health will occur, plus an adequate margin-of-safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of scientific ambiguity, OEHHA shall use criteria most protective of public health and shall incorporate uncertainty factors of noncarcinogenic substances for which scientific research indicates a safe dose-response threshold.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed periodically and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. For this reason PHGs are only one part of the information used by DHS for establishing drinking water standards. PHGs established by

OEHHA exert no regulatory burden and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are developed for technical assistance to DHS, but may also benefit federal, state and local public health officials. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of environmental waters where additional concerns of bioaccumulation in fish and shellfish may pertain. Often environmental water contaminant criteria are more stringent than drinking water PHGs, to account for human exposures to a single chemical in multiple environmental media and from bioconcentration by plants and animals in the food chain.

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SUMMARY

A Public Health Goal (PHG) of 0.7 mg/L (700 ppb) for trichlorofluoromethane (FC-11) is developed. The current California Maximum Contaminant Level (MCL) for FC-11 in drinking water is 0.15 mg/L (150 ppb). The U.S. Environmental Protection Agency (U.S. EPA) has not developed a Maximum Contaminant Level (MCL). FC-11 has had a variety of applications in industry and in consumer products, but as of 1997, further production was banned in the United States (U.S.). Use of FC-11 is on the decline, and as stocks are depleted, new emissions may eventually be eliminated. FC-11 is detected globally in ambient air, and was detected in small and large water systems in California during 1986 to 1987 at concentrations ranging from 0.3 to 19.45 μg/L. Toxic effects of FC-11 include cardiac and pulmonary disturbances (e.g., cardiac arrhythmias, tachycardia and hypotension) and changes in respiratory rate, minute volume, tidal volume and pulmonary compliance. Other effects include hepatic lesions, central nervous system dysfunction, skin and eye irritation and inflammation. Chronic exposure experiments in animals were negative for carcinogenicity. No information on the possible reproductive, teratogenic, mutagenic or carcinogenic effects in humans was found in the available literature. No sensitive populations were identified. There are no data suggesting increased sensitivity for infants and children. A lowest-observed-adverse-effect-level (LOAEL) of 1,802 mg/kg-day for liver effects and changes in blood chemistry (blood urea nitrogen) was identified from a subchronic inhalation study in dogs. Using this subchronic inhalation LOAEL, a PHG for FC-11 of 0.7 mg/L (700 ppb) is calculated.

INTRODUCTION

FC-11 was one of the most widely used chlorofluorocarbons in industrial applications such as a blowing agent in foam production and as an aerosol propellant. Since 1996 it is no longer being produced in the U.S., although the use of existing stocks is still permitted. Emissions are declining as a result of the production ban.

This document is a revision and reassessment of a 1989 California Department of Health Services (DHS, 1989) document entitled *Proposed Maximum Contaminant Level: Trichlorofluoromethane (FC-11)*. The DHS (1989) document calculated a Proposed Maximum Contaminant Level (PMCL) of 0.15 mg/L for FC-11 in drinking water. Scientific literature newly available since the publication of the 1989 DHS document were reviewed and any significant information was considered in reviewing the adequacy of the PMCL for public health protection. Additional research reported since 1989 is limited, with some new reports of human hazard following accidental exposure, but little new experimental data.

Exposure standards for drinking water or ambient air have not been developed by the U.S. Environmental Protection Agency (U.S. EPA).

CHEMICAL PROFILE

FC-11 is a colorless, stable, organic liquid at temperatures below 23.8°C. Chemical identification information is presented in Table 1. Pertinent physical and chemical properties of FC-11 are listed in Table 2.

Table 1. Chemical Identification

CAS Registry Number:	75-69-4 (Tatken and Lewis, 1983).
RTECS Number:	TB6125000 (Tatken and Lewis, 1983)
Synonyms:	Fluorotrichloromethane, fluorocarbon 11, NCI-C04637, chlorofluoromethane (CC13 F) Eskimon 11, F1 1B, fluorocarbon no. 11, fluorochloroform, Freon MF, Freon R11, FC-11, Frigen 11A, Frigen-11, FC-11, halocarbon, FRU 11, Propellant 11, monofluorotrichloromethane, R11 (refrigerant), R11 halocarbon (Sax and Lewis, 1985).
Trade Names:	Arcton-9, Frigen-11, Genetron, Isotron, Freon, Racon, Uncon, Fell, Eskimon 11, FC-111, Genetron 11, Isceon 131, Isotron 11, Ledon.

USE AND PRODUCTION

The reported total demand for all chlorofluorocarbons (CFCs) in the U.S. in 1985 was 458,000 tons (EHC 113, 1990). The three major CFCs, trichlorofluoromethane (FC-11), dichlorodifluoromethane (FC-12) and trichlorotrifluoroethane (FC-113), accounted for 83% of the total CFCs produced in the U.S. in that year. However, many of the uses for FC-11 have become increasingly restricted or banned (particularly as an aerosol propellant) due to its action as a stratospheric ozone depleter. As a result of the Montreal Protocol, production of fully halogenated CFCs in industrialized countries ended prior to 1996. FC-11 was used as a blowing agent in the production of polyurethane foams, refrigerant, degreasing agent, solvent, fire extinguishing agent, aerosol propellant and as a chemical intermediate. FC-11 production dropped 74% in 1994 due mainly to its replacement by hydrochlorofluorocarbons, such as HCFC-141b, which have a much lower ozone-depleting potential (C&EN, 1995). All FC-11 that is produced will eventually be released to the environment as emissions. General population exposure occurs by inhalation in ambient air. Occupational exposure occurs via inhalation and dermal contact.

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Human exposure to FC-11 that is attributable to water-based sources is difficult to assess accurately for California because complete analytical data are not available for most water systems. Estimates of human doses in this PHG document are based on the 1986 statewide survey of organic chemical contaminants in ground water of large water systems, as determined by analyses mandated by California Statute (DHS, 1986). The data on levels of FC-11 contamination in domestic water wells are used to estimate the current average concentration of FC-11 in the tap water supplied from these contaminated wells.

Three exposure pathways are used to estimate the total dose of FC-11 received by individuals in dwellings with contaminated tap water. They are ingestion (through drinking), inhalation (FC-11 volatilized from showers and other water uses) and dermal contact (through bathing and washing). The composite exposure through the three pathways (using appropriate absorption factors) is used

Table 2. Physical and Chemical Properties of FC -11 (DHS, 1989)

Property		**Reference**
Molecular formula	CCl_3F	Verschueren (1983)
Structural formula	Cl | Cl C F | Cl	Sax and Lewis (1985)
Molecular weight	137.38	Merck Index (1997)
Boiling point	23.8°C	Verschueren (1983)
Melting point	-111°C	Verschueren (1983)
Density	1.494 g/mL at 17.2°C	Merck Index (1997)
Vapor pressure	687 mm Hg at 20°C 980 mm Hg at 30°C	Verschueren (1983)
Henry's Law constant	0.11 atm-m^3/mol at 20°C	Mabey *et al.* (1982)
Conversion factors	1 ppm = 5.7 mg/m^3 1 mg/m^3 = 0.18 ppm	Verschueren (1983)
Solubility in water	1100 mg/L at 20°C	Sittig (1980)
Log octanol/water partition	2.53	Sax and Lewis (1985)
Partition coefficients at 25°C olive oil/gas serum/gas	 27 0.9	Morgan *et al.* (1972)
Appearance/odor	Colorless liquid or gas with chlorinated solvent odor, odor detection above 20% in air	Sittig (1985)

to calculate a daily time-weighted lifetime dose factor which, when multiplied by the FC-11 concentration in water, gives the estimated daily dose from all three pathways over a lifetime for an average individual representative of an exposed population.

An average worldwide background concentration of FC-11 in ambient air has been estimated at approximately 0.25 ppb (Cunnold *et al.*, 1986). Concentrations of up to 42 ppb have been detected in California near factories known to use large quantities of fluorocarbons (Hester *et al*., 1974).

No report of food contamination by FC-11 was found, but Dickson and Riley (1976) detected FC-11 in some marine organisms that may be used as food. The average concentrations on a dry weight basis for five species of fish and three species of mollusks were 1 to 6 µg/kg and 1.1 µg/kg, respectively.

In 1985, DHS carried out a statewide monitoring program for toxic organic chemicals in ground water in large systems (DHS, 1986). FC-11 was found in 3 of 2,949 wells analyzed at mean concentrations of 0.3 to 2.1 µg/L. During the period 1985 to 1988, 2,941 wells of small water systems were sampled (DHS, 1988). FC-11 was found in two wells each in Orange and Stanislaus Counties and in one well in Santa Barbara County at mean concentrations of 1.00 to 19.45 µg/L. The mean and median values were 6.27 and 3.20 µg/L. An estimated 4,095 persons were exposed to at least 0.3 µg/L FC-11, and 2,545 persons were exposed to 0.9 µg/L. An average dose for the exposed population of 6,640 has been estimated at 7.91×10^{-5} mg/kg-day (Reed *et al*, 1988).

DHS (1989) estimated that tap water-linked FC-11 exposures via inhalation, digestion and dermal absorption would be equivalent to ingesting between 7.93 L(mean) and 25.86 L (upper-bound estimate) of drinking water per day.

METABOLISM AND PHARMACOKINETICS

Absorption

No information regarding the kinetics or the extent of oral absorption of FC-11 was found in the available literature. In view of its nonpolarity, lack of ionizable functional groups and its high partition coefficients, it is likely that FC-11 is rapidly and completely absorbed following ingestion both in animals and in humans.

Inhalation is a common route of exposure to FC-11 and, as indicated by several studies conducted in humans (Morgan, 1972; Adir *et al*., 1975) and experimental animals (Azar *et al*., 1973; Blake and Mergner, 1974; Paulet, 1975a), the absorption of FC-11 via inhalation occurs rapidly. Morgan (1972) studied the absorption of [^{38}Cl]-FC-11 from the alveolar air of a male volunteer. The subject received a series of single inspiration exposures of approximately 7 mg [^{38}Cl]-FC-11, held his breath for 0 to 50 seconds, exhaled to clear the dead space and then exhaled the remaining air. The initial concentration of FC-11 in the alveolar air decreased rapidly. After 20 seconds, the concentration of FC-11 in the expired alveolar air was approximately 60% of the initial concentration.

Rapid transpulmonary absorption was observed in rabbits and dogs that received FC-11 via inhalation (McClure, 1972; Blake and Mergner, 1974; Paulet, 1975a). Using gas chromatography, McClure (1972) analyzed the arterial blood of dogs that received 25 actuations (17.5 mg/actuation); peak concentration in blood was reached in 15 seconds. Blake and Mergner (1974) also noted the rapid absorption of [^{14}C]-FC-11 in beagle dogs exposed to 4,500 to 5,500 ppm. The venous blood concentration reached a plateau within 20 minutes. Paulet (1975a) exposed rabbits and dogs to 2.5% or 5.0% FC-11 in air (25,000 or 50,000 ppm, respectively). Blood samples were taken from the carotid artery and analyzed by gas chromatography. The blood concentration at which equilibrium was established varied with the ambient concentration of FC-11. With rabbits and dogs administered 5% FC-11 in air, maximum carotid blood levels were reached within 10 minutes. Peak blood concentrations were higher in dogs (7.5 μg/mL) than in rabbits (1.5 μg/mL).

Angerer *et al.* (1985) exposed two women and one man to a mean concentration of 657 mg/m^3 FC-11 for 150, 264 and 210 minutes, respectively, corresponding to total absorbed doses of 1.08, 1.88 and 1.35 g (as calculated by the investigators). The blood concentration determined during the exposure ranged from 2.69 ± 0.27 to 2.87 ± 0.58 mg/L. Without specifying a time, the investigators stated that equilibrium was reached shortly after exposure. The investigators further concluded that the concentration of FC-11 in blood was independent of individual differences and duration of the exposure within the experimental range.

Adir *et al.* (1975) examined the pharmacokinetics of FC-11 in four beagle dogs. Samples of exhaled air and venous blood were collected during exposure and the concentrations were used to determine the parameters for a pharmacokinetic model. The percentage of absorbed FC-11 was calculated by comparison of the area under the blood-concentration-time curves generated from the model for inhalation exposure and simulated venous exposure. The investigators reported a calculated mean absorption of 82.4± 13.3% in humans and 76.9 ± 2.6% in dogs. Thus, an absorption factor of 76.9% is used in the PHG derivation to estimate exposure to beagle dogs (Jenkins and associates, 1970).

No information concerning the kinetics or the extent of dermal absorption of FC-11 was found in the available published literature. In view of its low polarity and high octanol/water partition coefficient, FC-11 is most likely absorbed by animals and humans following dermal exposure.

Distribution and Biotransformation

Quantitative information regarding the tissue distribution of FC-11 following inhalation absorption is available from studies in experimental animals. Azar *et al.* (1973) exposed dogs to 0.1, 0.5 or 1.0% FC-11 (1,000, 5,000 or 10,000 ppm, respectively) for 10 minutes. The arterial and venous blood concentrations were measured during the exposure period and for 15 minutes post exposure. The arterial concentration of FC-11 was higher during exposure whereas the venous concentration was higher during the post exposure period, suggesting that FC-11 was distributed to some tissues. This study provides some evidence that FC-11 may partition from the blood into tissues during exposure but that it does not accumulate in these tissues.

Tissue distribution of FC-11 and its metabolites in beagle dogs following inhalation exposure was studied by Blake and Mergner (1974). Male and female dogs were exposed to 1,040 to 5,500 ppm [^{14}C]-FC-11 for 6 to 20 minutes. Nonvolatile radioactivity was measured 24 hours after exposure using a drying and combustion method. The brain, lung, liver, heart and reproductive organs had higher amounts of radioactivity than other tissues; however, the total radioactivity represented less than 1% of the administered dose. FC-11 was also detected in the cerebrospinal fluid of dogs following two minutes of exposure (Paulet *et al.,* 1975a). Poklis (1975) investigated the tissue distribution of FC-11 in a male teenager who died as a result of the deliberate inhalation of FC-11. The tissue samples were homogenized and analyzed by gas chromatography. The highest concentration of FC-11 was found in the brain followed by liver, lung, blood, kidney, trachea and bile. These studies suggest that FC-11 and/or its metabolites cross the blood-brain barrier.

It has been shown that FC-11 interacts with hepatic microsomal cytochrome P_{450} systems to give a characteristic binding spectrum (Type I). Although Cox (1972a, 1972b) failed to detect dichlorofluoromethane in rat hepatic microsomal preparations incubated with FC-11, Wolf *et al.*, (1975) found that FC-11 was dechlorinated to dichlorofluoromethane under anaerobic conditions by rat hepatic microsomal preparations. Dechlorination was dependent upon the presence of NADPH and was proportional to the concentration of the microsomal protein.

Based on the available studies, it appears that very little FC-11 is metabolized *in vivo*. In male and female beagle dogs that were exposed to 1,040 to 5,500 ppm [^{14}C]-FC-11 in air, less than 0.5% of the administered radioactivity was detected in either the exhaled air as $^{14}CO_2$ or in the urine (Blake and Mergner, 1974). Similar findings were reported in humans by Mergner *et al.* (1975) who exposed one male and one female volunteer to 1,000 ppm [^{14}C]-FC-11 for 7.0 and 13.7 minutes, respectively. The recovery of radioactivity in the exhaled air that was attributable to $^{14}CO_2$ was approximately 0.12%. The radioactivity (nonvolatile) found in the urine accounted for approximately 0.08% of the initial dose. The investigators did not characterize the urinary metabolites.

Excretion

Paulet *et al.* (1975a) reported that FC-11 was eliminated primarily through the pulmonary system as the parent compound; bile and urine constituted only a minor pathway of excretion. Dogs (strain not specified) exposed to 0.26% FC-11 in air for 15 minutes had eliminated 84% of the initial dose through the pulmonary route 30 minutes after exposure. Morgan *et al.* (1972) exposed human subjects to FC-11 via inhalation, and by subtracting the amount of radioactivity exhaled from that administered, determined that about 23% of the administered FC-11 was retained in the body after 30 minutes. Mergner *et al.* (1975) reported that a male and a female volunteer exposed to 1,000 ppm vapor [^{14}C] FC-11 for 7 and 13.7 minutes, respectively, excreted a total of 79% (male) and 99% (female) of the parent compound through exhaled air. Within 60 minutes, the average total amount of [^{14}C]-FC-11 exhaled was 0.12%. The average amount of radioactivity recovered in the urine over a period of 72 hours was 0.08%. According to Blake and Mergner (1974) the elimination of FC-11 in dogs was extremely rapid, although the subsequent rate of elimination was slower. Less than 0.5% of the administered dose of [^{14}C]-FC-11 was detected in exhaled air and in urine. The recovery of administered radioactivity was close to 100%. In rabbits, very little FC-11 was eliminated in the urine and bile following inhalation of 5% FC-11 for 10 minutes (Paulet, 1975a). Forty minutes after exposure, respective totals of 0.68 µL and 0.38 µL FC-11 were found in the urine and bile, representing less than 1% of the initial dose.

A two-compartment model of elimination for FC-11 was proposed by McClure (1972). Based on the analysis of the arterial blood of dogs that received FC-11 via inhalation, the initial elimination half-time of FC-11 was 0.60 ± 0.25 minutes. In the two-compartment model of elimination in humans reported by Angerer *et al.* (1985), the half-times of elimination of FC-11 from blood and alveolar air during the initial phase were 7 and 11 minutes, respectively. During the second phase of elimination, half-times of 1.8 hours for blood and 1.0 hour for alveolar air were reported.

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

A single dose of 5 mL/kg (7.5 g/kg) of FC-11 administered to six female rats by gavage did not lead to any observed adverse effect (Slater, 1965). An approximate lethal concentration, which is defined as the minimum concentration in air leading to death in any of the animals over a given exposure period (SURC, 1974), of 6.6% FC-11 for four hours was reported in rats (Du Pont, 1961). Mortality occurred in adult white rats following inhalation exposure to FC-11 at 10% (within 20 to 30 minutes), 15% (within eight minutes), 20 to 30% (within four minutes) and 50% (within one minute) (Lester and Greenberg, 1950). Lethal doses of FC-11 are summarized in Table 3.

Aviado (1973) suggested that death was caused by respiratory failure, a generalized consequence of CNS depression caused by FC-11 (Aviado and Micozzi, 1981). Metabolic disturbance, as evidenced by a slight increase in both glucose and lactic acid concentration, occurred in dogs and rabbits exposed to 5% FC-11 in air for 20 minutes.

Narcosis has been associated with FC-11 inhalation exposure (Lester and Greenberg, 1950; Clark and Tinston, 1972). Successive disappearance of various reflexes with increasing FC-11 concentration was observed in adult white rats exposed to 6 to 9% FC-11 in air for up to 30 minutes (Lester and Greenberg, 1950). These effects included a loss of the postural reflex at 6% and 7%, a loss of both the postural and righting reflexes at 8%, and a loss of the postural, righting and corneal reflexes at 9% (Lester and Greenberg, 1950).

FC-11 affects the CNS in rats causing limb and head tremor, convulsions, narcosis, shallow respiration and death (Clark and Tinston, 1982). The median effective FC-11 concentration (EC_{50}) in air for these effects was estimated as 3.5% for a 10-minute exposure via inhalation (Clark and Tinston, 1982). Loss of coordination and slight tremor were observed in rats exposed to 3.6, 6.6 or 11.85% FC-11 in air for four hours; these effects were dose-dependent (Du Pont, 1961). Occasional tremor and chewing movements were also reported in Guinea pigs exposed to 2.5% FC-11 in air for 30 minutes; unconsciousness developed following exposure to 10% FC-11 for one hour (Nuckolls, 1933, as cited by Aviado, 1975b).

Cardiotoxicity associated with inhalation of FC-11 has been observed in various species of animals with and without anesthetization. Arrhythmias, tachycardia, depression of myocardial contractility and hypotension are well-documented responses to inhalation exposures to FC-11 (Aviado, 1975b).

Cardiac arrhythmias, characterized by atrial fibrillation, ventricular extrasystoles and widening of the T-wave developed in a dose-dependent manner in unanesthetized male Wistar rats exposed to 2.5, 5 or 10% FC-11 in air for five minutes (Watanabe and Aviado, 1975). Cardiac arrhythmias were also observed in anesthetized animals similarly exposed to FC-11 (Watanabe and Aviado, 1975). Spontaneous arrhythmias, heart rate depression and a reduction in the height of the QRS complex of the electrocardiogram (ECG) were observed in Swiss mice exposed to 10% FC-11 in air for four minutes (Brody *et al.*, 1974). Mice that received 10% FC-11 for six minutes were afflicted with second or third-degree atrioventricular block (Aviado and Belej, 1974). An elevation of the S-T segment and widening of the T-wave were observed in rats exposed to 5% or 10% FC-11 for five minutes (Watanabe and Aviado, 1975). Ventricular fibrillation was observed in one of three dogs two minutes after the onset of exposure to 10% FC-11 (Belej and Aviado, 1975). Signs of arrhythmia were observed in dogs exposed to various concentrations of FC-11 in air for 10 minutes (Flowers *et al.*, 1975). At 15%, a mild, transient sinus slowing was observed. At concentrations between 15% and 17.8% FC-11 in air, reversible sinus bradycardia developed in half of the 18 dogs, and sinus bradycardia, followed by escape beating and extrasystole, occurred in the other half. At 18% to 21.5% FC-11, similar rhythmic disturbances were also observed. A higher degree of atrioventricular block and death in all animals exposed occurred at 21.5% (Flowers *et al.*, 1975). Tachycardia developed in a dose-dependent manner in unanesthetized male Wistar rats that received 2.5, 5 or 10% FC-11 in air for five minutes (Watanabe and Aviado, 1975). In anesthetized animals, tachycardia was observed in dogs that received 1% FC-11 for five minutes within a 15-minute period (Belej and Aviado, 1975), in beagle dogs after two minutes of exposure to 2% FC-11 or within one or two minutes of exposure to 4% (Clark and Tinston, 1972), and in rhesus monkeys exposed to 5% FC-11 for five minutes within a 15-minute period (Aviado and Smith, 1975).

A decrease in myocardial contractility and cardiac output and an elevation in atrial pressure were observed in canine heart-lung preparations from dogs that received 2.5% or 5% FC-11 in air (Aviado and Belej, 1975). A depression of myocardial contractility was also observed in Rhesus monkeys exposed to 2.5% or 5% in air for five minutes within a 15-minute period (Belej *et al.*, 1974). In addition, a dose-dependent fall in aortic blood pressure was also observed (Belej *et al.*, 1974; Aviado and Smith, 1975). A reduction in mean aortic blood pressure was reported in anesthetized mongrel dogs that received 1% FC-11 in air for five minutes within a 15-minute period (Belej and Aviado, 1975a).

Respiratory irregularity and changes in respiratory rate, respiratory minute volume, tidal volume and pulmonary compliance have been reported in various species of animals exposed to FC-11. Respiratory irregularity was observed in dogs exposed to 1.0 to 2.97% FC-11 in air for four to five minutes (Du Pont, 1982). A reduction in respiratory rate occurred in male Osborne-Mendel rats within five minutes of the onset of exposure to 20% FC-11 (Friedman *et al.*, 1973) and in male Swiss mice that received 2.5% for four minutes (Brody *et al.*, 1974). Exposure to 3.6% FC-11 for four hours resulted in increased breathing rates in ChR-CD rats (Du Pont, 1961). A depression of respiratory minute volume was observed in male Swiss mice that were exposed to 2.5% FC-11 for four minutes (Brody *et al.*, 1974), in mongrel dogs that received 10% for 5 minutes (Belej and Aviado, 1975) and in Rhesus monkeys that received 5% for five minutes within a 15-minute period (Aviado and Smith, 1975). A decrease in tidal volume occurred in male Wistar rats that inhaled 2.5% FC-11 in air for two minutes (Watanabe and Aviado, 1975). Under the same exposure regimen, the decrease in tidal volume was less in rats suffering from emphysema than in healthy rats (Watanabe and Aviado, 1975).

Inhalation exposure to FC-11 resulted in decreased pulmonary compliance and increased pulmonary resistance in rats and mice (Brody *et al.*, 1974; Watanabe and Aviado, 1975). The opposite effect was observed in dogs and monkeys (Aviado and Smith, 1975; Belej and Aviado, 1975). A fall in pulmonary compliance was observed in male Wistar rats that inhaled 2.5% FC-11.

Table 3. Lethal Doses of FC-11 in Experimental Animals[1]

Route/Species (Strain)	Gender	Exposure Duration	Toxicity Value	Dose/ Concentration	Reference
Intraperitoneal					
Mice (NS)	male	NS	LD_{50}	1,743 mg/kg	Kudo *et al. (*1971)
	female	NS	LD_{50}	1,871 mg/kg	Kudo *et al. (*1971)
Inhalation					
Mice (NS)	NS	30 minutes	LC_{50}	10%	Paulet (1976)
Rats (Alderley Park)	NS	15 minutes	LC_{50}	13%	Clark and Tinston (1982)
Rats (NS)	NS	15 minutes	LC_{50}	13%	Du Pont (1982)
Rats (NS)	NS	30 minutes	LC_{50}	15%	Paulet (1982)
Rats (NS)	NS	4 hours	LC_{50}	2.62%	Du Pont (1982)
Rats (NS)	NS	4 hours	ALC	6.6%[2]	Du Pont (1961)
Guinea Pigs (NS)	NS	30 minutes	LC_{50}	25%	Paulet (1976)
Rabbits (NS)	NS	30 minutes	LC_{50}	25%	Paulet (1976)

1 The period of observation was not specified in any of the studies.
2 These values were converted from parts per million (ppm) to percent (%).
NS = not specified; ALC = approximate lethal concentration.

for two minutes (Watanabe and Aviado, 1975). Under the same exposure regimen, the fall in pulmonary compliance was more intense in rats suffering from emphysema than in normal rats (Watanabe and Aviado, 1975). A decrease in pulmonary compliance and an increase in pulmonary resistance developed in male Swiss mice that were administered FC-11 at 1% or 2% in air for four minutes (Brody *et al.,* 1974). A reduction in pulmonary resistance occurred in mongrel dogs administered FC-11 at 2.5% or 5% in air for five minutes within a 15-minute period, and an increase in pulmonary compliance occurred at 10% (Belej and Aviado, 1975). A depression of pulmonary resistance and an increase in pulmonary compliance were also observed in Rhesus monkeys exposed to FC-11 at 2.5% or 5% in air for five minutes within a 15-minute period (Aviado and Smith, 1975).

Trichloroethylene, perchloroethylene and 1,1,1-trichloroethane altered the normal ethanolamine phosphoglyceride fatty acid pattern in rat, gerbil and guinea pig brain, while FC-11 was without effect (Kyrklund and Haglid, 1990). Low uptake of FC-11 relative to the other chlorinated solvents was noted.

Subchronic Toxicity

Decreased blood urea nitrogen (BUN) and decreased oxygen consumption were observed in rats and rabbits that received 5% FC-11 in air, two hours/day for 15 days (Paulet *et al.,* 1975b). In contrast, elevated BUN was reported in male beagle dogs exposed to FC-11 via inhalation at either 1.025% eight hours/day, five days/week for six weeks or 0.1% continuously for 90 days (Jenkins *et al.,* 1970).

Neuronal edema and the formation of neuroglial vacuoles were observed in rats 11 days after a four hours/day, 10-day subacute inhalation exposure at 1.2% FC-11 (Du Pont, 1961).

Gross and histopathological alterations in the lung following FC-11 exposure have been reported (Clayton, 1966; Jenkins *et al.*, 1970). Emphysema and lung edema were observed in rats 11 days after a 10-day exposure (four hours/day) to 1.2% FC-11 (Du Pont, 1961). Edema was observed in rats exposed to either 6.6% or 11.8% for four hours (Du Pont, 1961). Pulmonary congestion was observed in guinea pigs that received 10% FC-11 for two hours (Nuckolls, 1933, as cited by Aviado, 1975b). Irritation, edema and slight inflammation of the skin were observed in rats sprayed with either FC-11 or a mixture of FC-11 and FC-12 (doses not specified for FC-l l or Freon-mix sprays) from 10 cm for 10 seconds twice daily, five days/week for six weeks (Clayton, 1967). The effects were more pronounced in those animals exposed to the FC-11/FC-12 mixture and in older rats.

Congestion of the eyeball and mild inflammation of the eyelid, accompanied by a fibrinous exudate, were observed in rabbits that received a five-second ocular spray of FC-11 from a distance of 20 cm, five days/week for one month (Quevauviller, 1966). Mild conjunctival irritation and inflammation were noted in rabbits that received ocular applications of FC-11 at either 15% in propylene glycol, 15% or 40% in dimethylphthalate, 50% in Nujol or as a nitrogen propelled aerosol (Du Pont, 1982). No permanent corneal damage was observed.

Beagle dogs were administered FC-11 at 5,000 ppm by volume of air over 90 consecutive days for six hours/day. No adverse effects on hematological or clinical biochemical parameters, including BUN were noted. Histological examinations failed to reveal any adverse findings. Similarly, adverse effects were not noted in Sprague-Dawley rats exposed to 10,000 ppm FC-11 in air for six hours/day over 90 days (Leuschner *et al.*, 1983).

Kudo *et al.* (1971) administered daily oral doses of 16.2, 54.5 or 218 mg/kg FC-11 to an unspecified number of male and female mice and observed them for one month. The investigators reported a slight decrease in food consumption and one case of liver cell vacuolation in the highest dose group.

In a study by Du Pont (1972), weanling albino ChR-CD rats were administered FC-11 via gavage at 5 or 30 mg/mL in corn oil for 90 days. Groups of 20 rats/sex were administered FC-11 once daily, seven days/week for the first four weeks, then once daily, five days/week until the end of the study. The average daily dose was calculated to be 41 to 73 mg/kg-day for the low-dose group and 245 to 450 mg/kg-day for the high-dose group. The control group consisted of 20 rats treated with the vehicle only. Animals were examined regularly for behavioral changes as well as changes in hematological, urinary and serum biochemical parameters including urea nitrogen, alkaline phosphatase, creatinine and glutamic-pyruvic transaminase. Body weight and feed consumption were recorded weekly. At the end of the study, 10 male and 10 female rats from each group were sacrificed and tissues were subjected to histological examination. No differences in nutritional, clinical, hematological, biochemical or histological indices were noted between the treated and vehicle control animals. In rats administered the high dose of FC-11, urinary fluoride excretion was elevated through week 11, after which no difference was observed between treated and control groups.

In the same study, groups of four male and four female one-year-old dogs (strain not specified) were administered daily 250 or 500 mg/mL FC-11 in corn oil via gelatin capsules , seven days/week for 90 days (Du Pont, 1972). The respective average daily doses were calculated as 40 to 69 and 170 to 346 mg/kg-day for the low and high-dose groups. The control group received capsules containing only corn oil. Toxicity was determined using the same indices described in the rat study. No nutritional, clinical, hematological, biochemical or histological evidence of toxicity was observed.

Jenkins *et al.* (1970) investigated the toxic effects of FC-11 in rats, dogs, monkeys and guinea pigs. Animals were exposed to FC-11 (99.98% purity) via inhalation either continuously at 1,008 ± 44 ppm for 90 days, or repeatedly at 10,250 ± 100 ppm for eight hours/day, five days/week, for six weeks. The following animals were used for both exposure regimens: NMR1:0(SD) Sprague-Dawley rats (eight males and seven females), beagle dogs (two males), and squirrel monkeys (*Saimi sciurea*) (nine males). NMR1:(ASH) Princeton-derived guinea pigs (eight males and seven females) were used in the continuous exposure study and Hartley guinea pigs were used in the repeated exposure study. Identical groups of animals served as controls. Hemoglobin concentration, blood cell counts, urea nitrogen concentration and alanine aminotransferase activity were determined for each animal pre- and post-exposure. In addition, activities of alkaline phosphatase, tyrosine aminotransferase, serum creatinine and urinary fluoride were determined for rats and guinea pigs, and sulfobromophthalein (BSP) concentration was determined for dogs. At the termination of the study, all animals were sacrificed. Tissues were examined for gross lesions, and histological examinations were performed on several organ tissues of several organs taken from all of the dogs and monkeys and from half of the rats and guinea pigs.

No significant differences (statistical test not specified) between pre-and post-exposure values in hematological and biochemical parameters were noted in any species except the dog. Dogs that received continuous or repeated exposures had respective elevations of 96% and 114% in serum urea nitrogen levels (the investigators did not specify whether this increase was significant, but it is significant according to the Student t-test, $p<0.05$). The investigators did not attribute this change to any specific organ or system injury. Histopathological changes in lung, kidneys, liver and heart were reported in a few treated animals, but the investigators stated that none of these was related to FC-11 exposure. The dose levels for the 90-day continuous exposure at 1,008 ppm were estimated to be 3023 mg/kg-day for rats [body weight (BW): 343 g, volumetric breathing rate (VBR): 0.220m^3/day)], 2240 mg/kg-day for guinea pigs (BW: 521 g, VBR: 0.248 m^3/day), 1920 mg/kg-day for dogs (BW: 11.3 kg, VBR: 4.61 m^3/day) and 3540 mg/kg-day for monkeys (BW: 624 g, VBR: 0.469 m^3/day). The dose levels for the six-week repeated exposure at 10,250 ppm were estimated to be 7440 mg/kg-day for rats (BW: 328 g, VBR: 0.214 m^3/day), 5400 mg/kg-day for guinea pigs (BW: 528 g, VBR: 0.250 m^3/day), 4830 mg/kg-day for dogs (BW: 10.1 kg, VBR: 4.28 m^3/day) and 8170 mg/kg-day for monkeys (BW: 722 g, VBR: 0.517 m^3/day).

Paulet *et al.* (1975b) studied the toxic effects of FC-11 and a Freon mixture (FC-11: FC-12, l0:90) in anesthetized rats and rabbits. Ten to 12 adult male Wistar rats and five adult rabbits (sex and strain not specified) were exposed via tracheas to 2.5% or 5% FC-11, or to a 5% Freon mixture for one hour twice daily for 15 days. Oxygen uptake, basal metabolic rate, respiratory quotient, blood serum electrolytes, serum glucose, cholesterol, lactic acid, alkaline reserve and liver glycogen were measured 10 days prior to, during and seven days after the exposures. No significant differences in any of the measured parameters were detected in either species exposed to 2.5% FC-11 or 5% Freon mixture. Both rats and rabbits exposed to 5% FC-11 had diuresis, as well as a decrease in BUN and oxygen and water consumption during treatment. The statistical significance of these changes was not discussed and data were not given, although the investigators stated that oxygen consumption decreased 44% and 25% in rats and rabbits, respectively. Hyperglycemia and hyperlactacidemia were detected in both species at 5% FC-11.

Reproductive and Developmental Toxicity

Maternal exposure of rats and rabbits to a 10:90 FC-11: FC-12 mixture did not result in developmental toxicity (Paulet, 1976). The animals were exposed to a 20% concentration of the Freon mixture for two hours/day, on days 4 to 10 of gestation for rats, and on days 5 to 20 of gestation for rabbits. No information on potential adverse developmental effects associated with FC-11 exposure alone was located in the available published literature.

Carcinogenicity and Chronic Toxicity

Epstein *et al.* (1967) conducted a one-year bioassay of FC-11 in male and female Swiss ICR/Ha mice. Four subcutaneous injections of 10% (v/v) FC-11 in tricaprylin were administered to the neck of neonatal mice: 0.1 mL was administered on days one and seven following birth, and 0.2 mL was administered on days 14 and 21 following birth. Control mice received corresponding volumes of vehicle. The survival rate was high. No evidence of carcinogenicity was reported at the end of the study.

In an experiment conducted by the National Cancer Institute (NCI, 1978), the potential carcinogenic activity of FC-11 was investigated in both sexes of rats and mice. Groups of 50 male and 50 female Osborne-Mendel rats received technical-grade FC-11 in corn oil by gavage at two dose levels, five days/week for 78 weeks. Males received either 488 or 977 mg/kg-day while females were administered either 538 or 1,077 mg/kg-day (time-weighted average). The rats were observed for an additional period of up to 33 weeks. The two control groups, 20 rats per sex per group, received either corn oil (vehicle controls) or were not treated (untreated controls). Time-adjusted statistical analysis of tumor incidence indicated no significant positive associations between FC-11 exposure and tumor incidence at any site in rats of either sex. A statistically significant increase in mortality was observed in male and female rats at both doses. Increased incidences of pleuritis and pericarditis were also observed in treated rats of both sexes compared with controls.

Groups of 50 male and 50 female B6C3F1 mice were treated similarly with technical-grade FC-11 in corn oil by gavage at two dose levels, five days/week for 78 weeks (NCI, 1978). The time-weighted average low and high doses for male and female mice were 1,962 and 3,925 mg/kg-day, respectively. The mice were observed for an additional 13 weeks. The two control groups, 20 rats per sex per group, received either corn oil (vehicle controls) or remained untreated (untreated controls). The survival was adequate for meaningful statistical analyses of late-developing tumors. The tumor incidences observed in the treated mice were similar to the incidences observed in the control mice. NCI concluded that, under the conditions of this bioassay, FC-11 was not carcinogenic to B6C3F1 mice. A statistically significant increase in mortality was observed in female mice.

Maltoni (1983) conducted an inhalation carcinogenicity study with Swiss mice (120 per sex). The animals were exposed to 1,000 or 5,000 ppm FC-11 for four hours/day, five days/week for 78 weeks. No increase in mortality or tumor frequency were observed. In a similar study with 120 Sprague-Dawley rats/sex, with FC-11 exposures of four hours/day, five days/week for 104 weeks, no increase in mortality or tumor frequency was noted.

Genetic Toxicity

The available data indicate that FC-11 is not mutagenic in the Ames *Salmonella* assay. FC-11 was negative in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 in the presence or absence of a rat hepatic microsomal activation system (S-9) (Du Pont, 1977). In a large-scale screen of 255 chemicals, Zeiger *et al.* (1987) also reported negative results in the Ames *Salmonella* assay in strains TA98, TA100, TA1535 and TA1537 and/or TA97, in the presence or absence of a hepatic activation system (S-9) obtained from rats or hamsters. Uehleke *et al.* (1977) incubated 3.6 moles of [^{14}C]-labeled FC-11 with a liver microsomal activating system obtained from either mice or rats pretreated with phenobarbital. No mutagenic activity was reported in *S. typhimurium* strains TA1535 and TA1538. Uehleke *et al.* (1977) found that incubation of [^{14}C]-FC-11 with liver microsomes and NADPH resulted in irreversible binding of radioactivity to endoplasmic protein and lipid. FC-11 was not mutagenic in either the presence or absence of a rat hepatic activation system (S-9) in the Chinese hamster ovary (CHO/HGPRT) cell assay (Krahn *et al.,* 1982).

Toxicological Effects in Humans

Most of the information on the toxic effects of FC-11 in humans has been obtained from case reports involving individuals who had accidentally or intentionally inhaled lethal or near-lethal concentrations of FC-11 propellant in aerosol products. No epidemiological studies regarding occupational or environmental exposure to FC-11 were available. Abuse of aerosol products containing FC-11 has resulted in sudden death, often following physical exertion (Baselt and Cravey, 1968; Bass, 1970; Aviado, 1975a; Standefer, 1975; Garriott and Petty, 1980). In most instances cardiac arrest was the stated cause of death. Acute pulmonary congestion was identified in some cases but no demonstrable pathology was observed in the majority of cases (Garriott and Petty, 1980; Brands, 1987).

A case of lethal poisoning due to FC-11 inhalation was reported by Groppi *et al.* (1994). FC-11 was detected in heart, lung, brain, liver, blood, kidney and spleen, with highest concentration in heart. The authors suggest the death was due to either sensitization of myocardium to catecholamines and resultant arrhythmia and cardiac arrest, or hypoxemic asphyxiation due to the saturation of the atmosphere by FC-11 in a closed environment.

Two patients exhibited adverse reactions that were attributed to FC-11 used as a propellant for metered-dose inhalers. These inhalers are used in treating bronchoconstriction due to asthma and chronic bronchitis (Oenbrink, 1993).

Normal use of household aerosols containing FC-11 by 20 women for four weeks resulted in no clinical changes in patient hemograms, biochemical profiles or respiratory parameters (Marier *et* *al.*, 1974). Stewart *et al.* (1978) were unable to detect changes in subjective and physiological responses in volunteers experimentally exposed to single doses of FC-11.

DOSE-RESPONSE ASSESSMENT

U.S. EPA has not developed health advisory values specifically for FC-11 in drinking water. A U.S. EPA Ambient Water Quality Criteria concentration for human health for halomethanes as a class has been published. This value, based on exposures to other halomethanes associated with a theoretical individual excess cancer risk level of 10^{-6}, is 0.19 µg/L. This value is cited by U.S. EPA in its Integrated Risk Information System (IRIS) for FC-11, but given the negative results of FC-11 carcinogenicity studies, its applicability to FC-11 is questionable. U.S. EPA has developed an oral reference dose of 0.3 mg/kg-day (U.S. EPA, 1997). The drinking water action level recommended by the DHS is 0.15 mg/L (DHS, 1987).

The current Occupational and Safety and Health Administration's (OSHA's) eight-hour time-weighted average (TWA) occupational standard is 5,600 mg/m^3 (DHS, 1989).

There is no adequate human dose-response information available to determine a no-observed-adverse-effect-level (NOAEL) for a PHG calculation. Therefore, the NOAEL or LOAEL values for FC-11 are derived from animal studies. However, most of these studies were not adequately designed to provide good dose-response data (i.e., less than an ideal number of dose groups were used and/or the sample size was small or unspecified). For the purposes of calculating a PHG for FC-11, each NOAEL or LOAEL identified from an inhalation exposure study was converted to mg/kg or mg/kg-day (in parentheses) based on assumptions of absorption, body weight (as reported in the original article), and volumetric breathing rate (VBR) calculated using the respiration and circulation data given by Altman and Dittmer (1974).

The National Academy of Sciences (NAS) considered the highest dose level (218 mg/kg) reported by Kudo *et al.* (1971) as an LOAEL based on decreased food consumption and liver cell vacuolation. A seven-day suggested-no-adverse-response-level (SNARL) for FC-11 in drinking water for a 70 kg adult consuming 2 L/day was calculated by NAS to be 8.0 mg/L by use of an uncertainty factor (UF) of 1,000 (NRC, 1980).

A 90-day oral NOAEL of 450 mg/kg-day for albino ChR-CD rats was noted from the gavage data of Du Pont (1972). A 90-day oral NOAEL of 346 mg/kg-day for dogs was obtained from the same study. This unpublished study contains a number of shortcomings and inconsistencies which reduces its usefulness for quantitative risk assessment.

Six-week inhalation NOAELs and/or LOAELs for FC-11 in rats, dogs, monkeys and guinea pigs were reported by Jenkins *et al.* (1970). Dogs that received continuous or repeated exposures (two animals per group) had respective elevations of 96% and 114% in serum urea nitrogen levels (significant according to Students t-test, $p<0.05$). The investigators did not attribute this change to any specific organ or system injury. Histopathological changes in lung, kidneys, liver and heart were reported in a few treated animals, but the investigators stated that none of these was related to FC-11 exposure. No adverse effects were noted for the other species. These data were interpreted as presenting an NOAEL for rats, guinea pigs and monkeys and an LOAEL for dogs. The dose levels for the 90-day continuous exposure at 1,008 ppm were estimated as 3020 mg/kg-day for rats (BW: 343 g, VBR: 0.220 m^3/day), 2240 mg/kg-day for guinea pigs (BW: 521 g, VBR: 0.248

m^3/day), 1920 mg/kg-day for dogs (BW: 11.3 kg, VBR: 4.61 m^3/day) and 3540 mg/kg-day for monkeys (BW: 624 g, VBR: 0.469 m^3/day).

LOAELs of 5% FC-11 in air for rats and rabbits for the development of hyperglycemia and hyperlactacidemia were reported (Paulet *et al.*, 1975b). The NOAEL for both species was 2.5% FC-11 in air. The doses at this level are estimated as 7180 mg/kg-day for a 225 g rat with a VBR of 0.166 m^3/day and 3270 mg/kg-day for a 3.25 kg rabbit with a VBR of 1.093 m^3/day.

A 90-day (six hours/day) inhalation NOAEL of 5,000 ppm FC-11 was reported by Leuschner *et al.* (1983). For Sprague-Dawley rats, a 90-day (six hours/day) inhalation NOAEL of 10,000 ppm was observed. No higher doses were tested.

The 90-day inhalation study in dogs reported by Jenkins *et al.* (1970) was considered the best available study for noncarcinogenic threshold estimation. The reported LOAEL for this study was 1,008 ppm (1920 mg/kg). The significance of this LOAEL is somewhat uncertain. The authors did not consider these findings as clear evidence of liver toxicity in the absence of other observed adverse effects, such as abnormal histopathological findings. However, the effect on serum urea nitrogen noted may represent a sensitive measure of mild adverse effects. In another similar study no changes in BUN were noted in beagle dogs receiving TWA inhalation exposures of 1,250 ppm over the same duration (Leuschner et al., 1983). Therefore, the 1,008 ppm level was considered to be a mild subchronic LOAEL for the purposes of calculating a PHG for FC-11.

CALCULATION OF PHG

A public health-protective concentration (C) for FC-11 in drinking water (in mg/L) can be calculated using the general equation for noncarcinogenic endpoints:

$$C = \frac{\text{LOAEL x BW x RSC}}{\text{UF x Leq/day}} = \text{mg/L}$$

where,

LOAEL	=	Lowest-observed-adverse-effect-level (used where an NOAEL is unavailable) of 1,008 ppm FC-11 in air
BW	=	Adult male body weight (70 kg).
RSC	=	Relative source contribution of 40% (0.4)
UF	=	Uncertainty factor of 3,000 (3-fold for LOAEL to NOAEL conversion, 10-fold for inter-species extrapolation, 10-fold for human variability and 10-fold for the use of a subchronic exposure study for lifetime exposures)
Leq/day	=	Volume of water consumed by an adult presenting FC-11 exposures equal to those from multipathway tap water exposures, including airborne and dermal exposures. DHS (1989) calculated multipathway tap water exposures to be equivalent to those from drinking 7.93 or 25.86 L/day, using mean and upper-bound assumptions, respectively.

The inhalation LOAEL value of 1,008 ppm was converted to 1,802 mg/kg-day as follows:

$$1{,}008 \text{ ppm x } 5.7 \text{ mg/m}^3\text{/ppm} = 5{,}746 \text{ mg/m}^3$$

Assuming a ventilation rate of 4.61 m^3/day for a 11.3 kg dog:

$$\text{Daily dosage} = \frac{5{,}746\ mg/m^3 \times 4.61\ m^3/day}{11.3\ kg}$$

$$= 2{,}344\ mg/kg\text{-}day$$

Assuming 76.9% (0.769) inhalation absorption, the daily absorbed dose is:

$$2{,}344\ mg/kg\text{-}day \times 0.769 = 1{,}802\ mg/kg\text{-}day.$$

The uncertainty factors used in this analysis are consistent with U.S. EPA and Office of Environmental Health Hazard Assessment (OEHHA) practices, which more specifically acknowledge actual uncertainty in data extrapolations. For the critical effect in this case, an LOAEL of 1,008 ppm (1,802 mg/kg-day) from a subchronic study in dogs, an intermediate uncertainty factor of $10^{1/2}$, or 3.2 (rounded to 3), is applied for extrapolation from a mild LOAEL to an NOAEL, a factor of 10 is used for extrapolation of these data to humans, a factor of 10 is used to account for differences in effects from subchronic versus chronic exposure and another factor of 10 is to account for variation in susceptibility among humans, which is intended to allow for potential sensitive individuals or populations, including infants and children. An intermediate 3-fold factor has been used for mild and/or low incidence adverse effects of numerous other chemicals by USEPA and OEHHA, and was considered appropriate for FC-113.

Because of inhalation and dermal exposures, the mean dose exposure is calculated to include exposures from showering and other home uses of tap water. Mean and upper-bound estimates of FC-11 exposures from drinking tap water and from other inhalation, oral and dermal exposures from use of tap water have been estimated as being equivalent to that from ingesting 7.93 L and 25.86 L of tap water per day (DHS, 1989). Other assumptions used in the calculation of the PHG include an adult body weight of 70 Kg (for an adult male) and a relative source contribution of 40% (0.4) to account for other exposure to FC-11 besides those due to use of contaminated tap water. Of alternative exposure routes, exposures to contaminated ambient air are likely to be most significant. The use of 40% rather than 20% for an RSC is justified because exposures via other sources are expected to be minor. Tap water will also provide substantial additional exposure from FC-11 via volatilization (e.g., bathing, showering, cleaning, cooking).

Two public health-protective concentrations (C) are calculated incorporating either a mean estimate (C_{MEAN}) or an upper-bound estimate (C_{UB}) of multiple media (ingestion, inhalation and dermal absorption) exposure from tap water.

Therefore,

$$C_{MEAN} = \frac{1{,}802\ mg/kg\text{-}day \times 70\ kg \times 0.4}{3{,}000 \times 7.93\ Leq/day}$$

$$= 2.12\ mg/L = 2\ mg/L\ (\text{rounded}) = 2{,}000\ ppb.$$

Or,

$$C_{UB} = \frac{1{,}802 \text{ x } 70 \text{ kg x } 0.4}{3{,}000 \text{ x } 25.86 \text{ Leq/day}}$$

$$= 0.651 \text{ mg/L} = 0.7 \text{ mg/L (rounded)} = 700 \text{ ppb.}$$

The C_{UB} is proposed for use as the PHG, as the PHG is intended to ensure adequate protection of the health of sensitive human subpopulations. Therefore, OEHHA calculates a PHG for FC-11 in drinking water of 700 ppb.

RISK CHARACTERIZATION

Exposures to FC-11 may occur via inhalation, ingestion and dermal routes of exposure. Relatively low ambient levels are expected in most settings (0.25 ppb) while higher levels may occur near facilities using the substance (up to 42 ppb) (Cunnold *et al.*, 1986; Hester *et al.*, 1974). Lower exposures are generally expected via ingestion and dermal routes. Production of FC-11 in the U.S. ceased in 1996, and exposures are expected to decline as the use of FC-11 is phased out. Previously reported exposures are much lower than those identified as potentially hazardous in this document.

Major uncertainties in the dose-response assessment and the derivation of the PHG include the lack of adequate human health effects data and the limited lifetime exposure and reproductive studies in animals. There are uncertainties regarding the relative contribution of water-borne exposures as compared with inhalation and other routes of exposure. The key study selected is limited by its small sample size, lack of multiple dose groups, and lack of exposed female subjects. In general, reports of adverse effects associated with human exposure to FC-11 have been relatively few and as use and emissions of FC-11 decline, the potential for human harm will also lessen.

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